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(54) **ISONITRILE RADIONUCLIDE COMPLEXES FOR LABELLING AND IMAGING AGENTS.**

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(73) Proprietor: **PRESIDENT AND FELLOWS OF HARVARD COLLEGE**
17 Quincy Street
Cambridge Massachusetts 02138 (US)
(73) Proprietor: **MASSACHUSETTS INSTITUTE OF TECHNOLOGY**
77 Massachusetts Avenue
Cambridge, MA 02139 (US)

(72) Inventor: **JONES, Alun G.**
50 Manemet Road
Newton Centre, MA 02159 (US)
Inventor: **DAVISON, Alan**
30 Tillotson Road
Needham, MA 02194 (US)
Inventor: **ABRAMS, Michael J.**
74 Brainerd Road
Allston, MA 02134 (US)

(74) Representative: **Schwabe, Hans-Georg, Dipl.-Ing. et al**
Patentanwälte Schwabe, Sandmair, Marx
Stuntzstrasse 16
D-8000 München 80 (DE)

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Descripti n

This invention relates to novel isonitrile complexes of radionuclides, i.e., for example, of radioactive isotopes such as ^{99m}Tc, ^{99}Tc, ^{97}Ru, ^{51}Cr, ^{57}Co, ^{188}Re, and ^{191}Os. The complexes can readily be prepared and isolated at both macro and tracer concentrations in aqueous media, together with any of a wide variety of counterions, as appropriate. They display remarkably effective labelling characteristics for liposomes or vesicles, and a variety of living cells containing lipid membranes, and are also effective imaging agents for detecting abnormalities in the tissues of various organs as well as the existence of blood clots. The complexes of ^{99m}Tc are particularly preferred because of the desirable nuclear properties of this radioisotope, i.e., its half-life and gamma ray energy.

A variety of radioisotope imaging and labelling agents have been developed in the past; however, the complexes previously available have generally suffered from the shortcomings of high cost, complexity of the method of preparation, or failure to exhibit high quality imaging or highly effective labelling because of insufficient lipophilic properties.

Isonitrile complexes of various non-radioactive metals have been described but there has been no suggestion that isonitrile complexes of radionuclides would have properties making them desirable or useful as imaging or labelling agents. Oxine complexes of ^{99m}Tc have been described for use in labelling platelets. Wistow et al., *J. Nucl. Med.*, Vol. 19, 483—487 (1978). The direct labelling of red blood cells with ^{99m}Tc by a reductive process, and the use of the labelled cells for imaging have been described. Smith et al., *J. Nucl. Med.*, Vol. 17, 126—132 (1976). Various complexes of ^{99m}TC with arsenic- and phosphorus-containing organic compounds have been proposed for use as imaging and labelling agents. Deutsch et al., *Science* , Vol. 214, 85—86 (1981); *J. Nucl. Med.*, Vol. 22, 897—907 (1981); European Pat. Appln. No. 81400618.5, published Oct. 28, 1981, Pubin. No. 0038756.

Because of the general availability of supplies of ^{99m}Tc in clinical laboratories in the form of pertechnetate as well as the desirable half-life and gamma ray energy of this radionuclide, the complexes of the present invention preferably contain ^{99m}Tc, although complexes with other radionuclides as indicated are also embraced within the scope of the invention as stated above. Moreover, the general availability of supplies of pertechnetate make it convenient to use kits for preparation of the complexes of ^{99m}Tc according to the present invention.

The present invention consequently comprises a coordination complex of an isonitrile ligand represented by the formula:

$$[A((CN)_xR)_yB_zB'_{z'}]n$$

in which A is a radionuclide selected from radioactive isotopes of Tc, Ru, Co, Pt, Fe, Os, Ir, W, Re, Cr, Mo, Mn, Ni, Rh, Pd, Nb and Ta, for example, ^{99m}Tc, ^{99}Tc, ^{97}Ru, ^{51}Cr, ^{57}Co, ^{188}Re and ^{191}Os; $(CN)_xR$ is a monodentate or polydentate isonitrile ligand bonded to the radionuclide through the carbon atom of the CN group; R is an organic radial; B and B' are independently other ligands selected from solvents such as water, halogen atoms such as chlorine or bromine atoms, and ligands comprising one or more neutral donor atoms capable of forming bonds with said radionuclide; x and y are each independently, integers from 1 to 8; z and z' are each independently 0 or an integer from 1 to 7; with the proviso that (xy)+z+z' is less than or equal to 8; and n indicates the charge of the complex and can be 0 (neutral), or a positive or negative integer the value of which depends upon the valence state of A, and the charges on R, B and B'. Any desired counterion can be present as required by the charge on the complex with the proviso that such counterion must be pharmaceutically acceptable if the complex is to be used *in vivo*.

In the above formula, R is an organic radical that can have additional neutral donor atoms capable of forming coordinate bonds with the radionuclides. If such additional donor atom(s) are used, the number of such donor atom(s) should be added to x to determine z and z' within the aforementioned constraint that (xy)+z+z' are less than or equal to 8.

A neutral donor atom is defined as an atom having a free-electron pair available for accepting a proton to provide a charged ligand or for complexing with a radionuclide to form a coordination complex. Examples of neutral donor atoms suitable for use in this invention include, for example, arsenic, phosphorus, nitrogen, sulfur, oxygen, selenium and tellurium.

Although complexes of this invention can be neutral, or positively or negatively charged, the class of lipophilic cationic complexes is presently preferred.

Any desired counterion may also be present in the composition, such as, in the case of cationic complexes, chloride, fluoride, bromide, iodide, hydroxide, sulfate or bisulfate, dihydrogen phosphate, fluoroborate, hexafluorophosphate. Depending upon the particular radionuclide, the valence state and other conditions for complexing, a particular radioactive metal can have from one to eight isonitrile ligands bonded thereto. As aforesaid, each isonitrile ligand is bonded to the radionuclide through the isonitrile carbon atom. Preferably, the complexes of this invention are kinetically inert, and hence stable products. H wever, the complexes need nly be sufficiently stable for the intended use.

The organic radical R can be aliphatic or aromatic and may be substituted with a variety of groups which may or may not be charged. When th rganic radical R carries a charged substituent group, the charge n the resultant complex is th summation of th charges of the ligands (R, B and B') and the charge

of th radionuclide. Among the aromatic R groups which may b present are phenyl, tolyl, xylyl, naphthyl, diphenyl and substituted aromatic groups containing such substitu nts as halo, e.g., chloro, bromo, iod or fluoro; hydroxy, nitro, alkyl, alkoxy; among the aliphatic R groups which may be present are alkyl, preferably containing 1 to 20 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-hexyl, 2-ethylh xyl, dodecyl, stearyl. Substituent groups may also be present in the aliphatic groups, including among others the same substituent groups as those listed above for aromatic groups.

When the isonitrile ligand is a polydentate ligand such as, for example, a bidentate ligand having the structure CNRNC, the organic radical portion of the ligand can be a divalent radical derived from a group as defined for R above. In such case the number of isonitrile ligands required for each complex is appropriately reduced.

In general, because the desired lipophilic characteristics in the complex can be achieved without the need for substituent groups, it is preferred for the sake of simplicity to employ unsubstituted hydrocarbon groups as the R groups. However, the lipophilic characteristics of the complex can be further varied by varying the R groups to adapt the complex for labelling selected materials, for membrane transport such as for the blood-brain barrier, or for imaging selected organs and dynamic processes related to their function.

In one embodiment, the complex of the present invention is a homoleptic six coordinate (hexakis) cationic complex having the formula

$$[A(CNR)_6]^+$$

in which A is a monovalent radionuclide selected from technetium, or ^{188}Re, CNR is a monodenate isonitrile ligand, and R is an organic radical as defined above. A suitable counterion such as described above is also present.

For the purposes of this invention, useful radionuclides are radioactive metals having decay properties that are amenable for use as a tracer.

The invention further comprises a kit for converting a supply of a radionuclide, e.g. ^{99m}Tc-pertechnetate to a complex as stated above, said kit comprising an isonitrile ligand as defined above and a reducing agent capable of reducing the radioactive metal to form the coordination complex.

The complexes of the present invention can easily be prepared by admixing a salt of the radioactive metal and the isonitrile ligand in the presence of a suitable reducing agent, if required, in aqueous media at temperatures from room temperature to reflux temperature or even higher, and are obtained and isolatable in high yield at both macro (carrier added, e.g. ^{99}Tc) concentrations and a tracer (no carrier added, e.g. ^{99m}Tc) concentrations of less than 10^{-6} molar. In some cases the isonitrile ligand can itself act as the reducing agent thus eliminating the need for an additional reducing agent. Suitable additional reducing agents, when required or desired are well known to those skilled in the art. The reaction is generally complete with 5 minutes to 2 hours, depending upon the identity of the particular reagents employed. The radiolabelled complex is made in the same way as the corresponding non-radioactive isonitrile complex by simply substituting the desired radionuclide for the corresponding non-radioactive element in the starting materials, except in the case of technetium because all technetium isotopes are radioactive.

In the case of technetium such as, for example ^{99}Tc or ^{99m}Tc, a complex in accord with this invention is preferably made by mixing pertechnetate (Tc^{+7}) with the desired isonitrile in aqueous medium, then adding to the reaction mixture an appropriate reducing agent capable of reducing the technetium. Among suitable reducing agents are alkali metal dithionites, stannous salts, sodium borohydride, and others, as is well known.

The isonitrile technetium complexes of this invention can also be prepared from preformed technetium complexes having oxidation states for technetium of, for instance, +3, +4 or +5, by treating these preformed complexes with an excess of isonitrile ligands under suitable conditions. For example, the technetium-isonitrile complex can also be prepared by reacting the desired isonitrile ligand with the hexakis-thiourea complex of Tc^{+3} or with a technetium-glucoheptonate complex, or the like.

An excess of the isonitrile ligand, up to 50 to 100% molar excess or more, and an excess of reducing agent, can be used in the complexing reaction to ensure maximum yield from the technetium. Following the reaction, the desired complex can be separated from the reaction mixture, if required, by crystallization or precipitation or by conventional chromatography or ion exchange chromatography.

The following specific examples are intended to illustrate more fully the nature of the present invention without acting as a limitation upon its scope.

Example 1

Preparation of hexakis-(t-butyl isonitrile) technetium (I) hexafluorophosphate from $[Tc(III)(tu)_6]^{3+}$ where tu=thiourea

To a 500 ml round bottom flask were added a stir bar, 0.84 g of $[^{99}Tc(thiourea)_6]Cl_3$ (0.13 mmol), methan l (25 ml) and 0.1 g t-butyl isonitril (1.3 mmol). Th stired reaction mixture was refluxed for 1.5 h, and the resulting pale yellow soluti n transferred to a 100 ml beaker and water (40 ml) added. The volume was reduced to half by stirring and heating on a hot plate. Then 30 ml water was added and the volume reduced to a half as before.

The almost colorless solution was cooled to room temperature and 0.5g $[NH_4][PF_6]$ in water (10 ml)

added, precipitating a white solid which was collected by suction filtration. This was washed with water (10 ml) and eth r (10 ml), and dri d *in vacuo*.

Yield of $[(t\text{-}C_4H_9NC)_6{}^{99}Tc][PF_6]$ 0.06 g (0.08 mmol) equivalent to 62% based on Tc. MP=222°C

The complex is soluble in polar organic solvents and was recrystallized by slow evaporation from an acetone/water solution (4:1 v/v) giving white crystals.

Analysis for $C_{30}H_{54}F_6N_6PTc$

	C	H	N
Calc. (%)	48.50	7.34	11.32
found	48.60	7.25	11.32

Optical spectrum (in CH_3CN)
260 nm (shoulder)
235 nm $\varepsilon=8\times10^4$ $cm^{-1}mol^{-1}l$
Infrared (KBR)
ν (CN) =2080 cm^{-1} (strong)
Conductivity (CH_3CN; $10^{-3}M$
$\Lambda=140$ $ohm^{-1}cm^2mol^{-1}$
Field desorption mass spectrometry (positive ion mode)
m/z=597 (cation, C^+)

Examples 2—6
Standard preparation of $[(RNC)_6Tc]^+$cations at carrier added levels
Where R=—CH_3
—n—C_3H_7
—i-C_3H_7
—$C(CH_3)_3$
—cyclohexyl
—methyl
—n-propyl
—isopropyl
—tertiary butyl

To a 50 ml round-bottomed flask was added ethanol (10ml), water (10 ml, pH adjusted to 12 with NaOH), 2.5 ml RNC, 0.7 ml of 0.438 *M* ammonium pertechnetate $(NH_4)[^{99}TcO_4]$, and a stir bar. Sometimes, for convenience of analysis, the ^{99m}Tc isotope was used as a tracer. A second solution containing 0.21 g sodium dithionite ($Na_2S_2O_4$) in water (5 ml, pH 12) was prepared, and added dropwise to the first reaction mixture. The solution was brought to reflux using a heating mantle, and maintained for 15 minutes. A further 50 mg $Na_2S_2O_4$ solution were then added dropwise and the solution refluxed for a further 30 minutes.

The reaction mixture was transferred to a 100 ml beaker and the volume reduced to a half by boiling off solvent on a hot plate. Water (40 ml) was added and the solution cooled to room temperature. 0.5 g of $[NH_4][PF_6]$ in water (10 ml) was added, immediately, precipitating a white solid. This was collected by vacuum filtration, washed with water (10 ml) and ether (10 ml), and subsequently dried *in vacuo*.

Recrystallization from acetone/water yields white crystalline $[Tc(CNR)_6][PF_6]$ in approximately 90% yield with respect to technetium.

Examples 7—8
Tracer (no carrier added) synthesis of $[Tc(CNC(CH_3)_3)_6]^+$hexakis-(t-butyl isonitrile) technetium (I) cation
1. By sodium dithionite reduction

In a standard scintillation counting vial were mixed isotonic saline (2 ml) containing $^{99m}TcO_4^-$ obtained by elution of a $^{99}Mo/^{99m}Tc$ radionuclide regenerator, 2 drops of 1*N* NaOH solution, ethanol (2 ml), and a small stirring bar. Then, 65µl of t-butyl isonitrile were added. A second solution of 20 mg sodium dithionite ($Na_2S_2O_4$) freshly dissolved in water (pH adjusted to 12 with NaOH) was prepared and this solution added to the first.

The mixture was stirred for 15 minutes and then transferred to a siliconized 50 ml round bottomed flask fitted with a vacuum adaptor. Solvent was removed *in vacuo* using heat from an infra-red lamp. The residue was washed with ethanol (100 µl) and then with isotonic saline (1 ml). This solution then contained the isonitrile complex in a form suitabl for administration to animals. The product of reaction was analyzed by HPLC (high pressure liquid chromatography) before use.

2. By sodium glucoheptonate reduction

A commercially available stann us glucoheptonate radi pharmaceutical kit (Glusoscan ™, New

England Nuclear Corporation) was reconstituted using isotonic saline (5 ml). Th r sulting solution was withdrawn using a syringe and added to 2 mg $SnCl_2 \cdot 2H_2O$ in a scintillation vial. Th mixture was stirred for five minutes, and 1 ml withdrawn and added to a siliconized Vacutainer™ tube containing t-butyl isonitrile (20 µl), ethan l (120 µl), and a small stirring bar. The mixture was stirred for several minutes and then filtered through a 0.22 µm Millipore® filter into a second siliconized tube. To the resulting clear solution was added isotonic saline (0.5 ml) containing an appropriate level of $^{99m}TcO_4^-$ obtained by eluting a commercial radionuclide generator. The solution was stirred for five minutes.

Extraction of the product

This step may be used with either of the above syntheses to provide a pure sample of the isonitrile complex free from the other materials in the syntheses.

The solution was transferred to a separatory funnel (50 ml) and twice extracted with methylene chloride (3 ml). The organic phase was twice washed with isotonic saline (5 ml) and then transferred to a siliconized round-bottomed flask (50 ml) fitted with a vacuum adaptor. The solvent was removed *in vacuo*, aided by heating with an infra-red lamp. The flask was washed first by addition of ethanol (100 µl) followed by saline (1 ml). The solution was then ready for administration to animals after assay by HPLC, the complex being in the form of a solution in a physiologically acceptable non-toxic carrier.

Both procedures can be used to prepare the other complexes of the invention. Those prepared include methyl, n-propyl, isopropyl, n-butyl, tert-butyl, and cyclohexyl isonitrile complexes of ^{99m}Tc.

Kits in accord with the present invention comprise a quantity of a reducing agent for reducing a preselected radionuclide. Preferably, such kits contain a predetermined quantity of an isonitrile ligand and a predetermined quantity of a reducing agent capable of reducing a predetermined quantity of a preselected radionuclide. It is also preferred that the isonitrile ligand and reducing agent be lyophilized to facilitate storage stability. The isonitrile ligand and reducing agent can be contained in a sealed, sterilized container.

In one embodiment of the invention, a kit for use in making the complexes of the present invention from a supply of ^{99m}Tc such as the pertechnetate solution in isotonic saline available in most clinical laboratories includes the desired quantity of a selected isonitrile ligand to react with a selected quantity of pertechnetate, and a reducing agent such as sodium dithionite in an amount sufficient to reduce the selected quantity of pertechnetate to form the desired complex.

Injection of the t-butyl isonitrile products of Examples 7 and 8 into animal models followed by conventional imaging procedures showed that vascular emboli can be detected in the lungs as well as in other parts of the vasculature, as described below. Following the detection by gamma camera of unidentified sites of localization in the lung field of apparently normal, healthy dogs, the fact that these represented blood clots was determined. Autologous clots prepared *in vitro* and labeled with small amount of ^{99m}Tc-sulfur colloid were introduced into the lung of a dog and their position determined by scanning. A large (several mCi) dose of ^{99m}Tc - *hexakis* - (tertiary - butylisonitrile) technetium (I) was injected and several of the clots were subsequently visualized. Computer analysis of the data collected showed conclusively that localization was occurring. Furthermore, analysis of the initial perfusion phase in the lung showed areas of deficit in blood flow associated with several of the emboli. Other experiments yielded similar results.

In other experiments isonitrile complexes of this invention were used to label liposomes; to label mammalian cells such as Chinese hamster V-79 lung fibroblast cells, leukocytes isolated from rabbit blood, and human erythrocytes (red blood cells); to visualize bone marrow; to measure lung function; and for mycardial imaging. For instance, both tertiary-butyl and isopropyl isonitrile products have been used to visualize myocardial tissue by external imaging.

Such cells and liposomes can be readily labeled by incubating the radiolabeled complexes of this invention with such cells or liposomes in a suitable medium and measuring the uptake of radioactivity in accord with the methods described by Kassis, A. I. et al., *J. Nucl. Med.*, Vol 21, 88—90 (1980). Incorporation of the radioactive complex can be as high as 29 pCi/cell. Studies have shown that the radioactive label can be 90% retained for up to sixteen hours. Autologous leukocytes separated from fresh rabbit blood were labeled with the ^{99m}Tc complex and subsequently reinjected into the rabbit. The distribution of the radiolabeled cells could be followed by gamma camera. Also liposomes have been labeled by similar techniques and their distribution in mice followed by a gamma camera.

Thus, it can be readily appreciated that complexes of this invention are useful not only in methods for visualizing cardiac tissue, but also in methods for detecting the presence of thrombi in the lung and associated areas of blood perfusion deficits, for studying lung function, for studying renal excretion, and for imaging bone marrow and the hepatobiliary system. The complexes are further useful in methods for radioactive tagging of cells and formed elements of blood, other animal cells, plant cells, and small organisms which possess membranous exteriors, e.g., single-cell entities, microbes, etc. In addition, they can be employed to label previously prepared liposomes with ut the necessity for encapsulation as is the case with many ther labelling agents Finally, complexes f the inventors can be employed in therapeutic methods.

Th choice of radi nuclides will depend on the use. For example, preferred radionuclides for diagn stic imaging are radioactive isotopes of Tc, Ru, Co, Pt, Fe, Os and Ir; preferred radionuclides for

therapeutic uses are radioactive isotopes of W, R , Fe and Os; preferred radionuclides for radioactive tagging are Cr, Mo, Co, Tc, Fe, Mn, W, Ru, Ni, Rh, Ir, Pd, Nb and Ta.

Claims

1. An isonitrile complex having the formula:

$$[A((CN)_xR)_yB_zB'_{z'}]n$$

wherein A is a radionuclide selected from radioactive isotopes of Tc, Ru, Co, Pt, Fe, Os, Ir, W, Re, Cr, Mo, Mn, Ni, Rh, Pd, Nb and Ta; $(CN)_xR$ is a monodentate or polydentate isonitrile ligand bonded to the radionuclide through the carbon atom of the CN group; R is an organic radical; B and B' are independently other ligands selected from solvents, halogen atoms, and ligands comprising one or more neutral donor atoms capable of forming coordinate bonds with said radionuclide; x and y are each independently, integers from 1 to 8; z and z' are each independently 0 or an integer from 1 to 7; with the provisio that (xy)+z+z' is less than or equal to 8; and n indicates the charge of the complex and can be 0 (neutral), or a positive or negative integer.

2. An isonitrile complex having the formula:

$$[A(CNR)_6]^+$$

wherein A is a radionuclide selected from technetium and ^{188}Re, and R is an organic radical.

3. A cationic lipophilic hexakis t-butyl isonitrile complex of technetium.

4. A complex as claimed in claim 1 in which said radionuclide is a radioactive isotope of Tc.

5. A complex as claimed in claim 1 in which said radionuclide is a radioactive isotope of Re.

6. A complex as claimed in claim 1 in which said isonitrile ligand is aliphatic.

7. A complex as claimed in claim 1 in which said isonitrile ligand is a hydrocarbon isonitrile.

8. A complex as claimed in claim 1 in which said isonitrile ligand is a saturated hydrocarbon isonitrile.

9. A complex as claimed in claim 1 wherein each coordinate position of said radioactive metal is filled by an isonitrile ligand.

10. A complex as claimed in claim 1 wherein said isonitrile ligand is a monodentate ligand.

11. A complex as claimed in claim 1 wherein said isonitrile ligand is a bidentate ligand.

12. A complex as claimed in claim 1 wherein said isonitrile ligand is tridentate ligand.

13. A complex as claimed in claim 1 wherein said complex is a cationic lipophilic complex.

14. A complex as claimed in claim 1 wherein said radionuclide is a radioactive isotope of Tc, Ru, Co, Pt, Fe, Os or Ir.

15. A complex as claimed in claim 1 wherein said radionuclide is a radioactive isotope of W, Re, Fe or Os.

16. A complex as claimed in claim 1 wherein said radionuclide is a radioactive isotope of Cr, Mo, Co, Tc, Fe, Mn, W, Ru, Ni, Rh, Ir, Pd, Nb or Ta.

17. A kit for preparing a coordination complex according to claims 1—3, said kit comprising a predetermined quantity of said isonitrile ligand and a predetermined quantity of a reducing agent capable of reducing a predetermined quantity of a preselected one of said radionuclides to form said complex.

18. A kit as claimed in claim 17 wherein said isonitrile ligand and said reducing agent are lyophilized.

19. A kit as claimed in claim 17 wherein said lyophilized isonitrile ligand and reducing agent are contained in a sealed, sterilized container.

20. A kit as claimed in claim 17, 18 or 19 wherein said preselected radionuclide is an isotope of Tc.

21. A kit as claimed in claim 17, 18 or 19 wherein said preselected radionuclide is an isotope of Re.

22. A kit for converting a supply of ^{99m}Tc-pertechnetate to a complex as claimed in claim 1—3, said kit comprising a supply of an isonitrile and a supply of a reducing agent capable of reducing technetium.

23. A kit as claimed in claim 22 in which said reducing agent is selected from dithionites and stannous salts.

24. A kit as claimed in claim 22 wherein said isonitrile ligand and said reducing agent are lyophilized.

25. A kit as claimed in claim 22 wherein said lyophilized isonitrile ligand and reducing agent are contained in a sealed, sterilized container.

26. A kit as claimed in claim 17 wherein said radionuclide is a radioactive isotope of Tc, Ru, Co, Pt, Fe, Os or Ir.

27. A kit as claimed in claim 17 wherein said radionuclide is a radioactive isotope of W, Re, Fe or Os.

28. A kit as claimed in claim 17 wherein said radionuclide is a radioactive isotope of Cr, Mo, Co, Tc, Fe, Mn, W, Ru, Ni, Rh, Ir, Pd, Nb or Ta.

29. A method for labeling a cell or liposome comprising incubating said cell or liposome with a coordination complex as claimed in claim 1 in a suitable medium.

Patentansprüche

1. Isonitril-Komplex mit der Formel

$$[A((CN)_xR)_yB_zB'_{z'}]_n$$

worin A ein Radionuklid bedeutet, das aus den radioaktiven Isotopen von Tc, Ru, Co, Pt, Fe, Os, Ir, W, Re, Cr, Mo, Mn, Ni, Rh, Pd, Nb und Ta ausgewählt ist; $(CN)_xR$ ein einzähliger oder vielzähliger Isonitrilligand ist, der an das Radionuklid durch das Kohlenstoffatom der CN-Gruppe gebunden ist, R ein organischer Rest ist; B und B' unabhängig voneinander andere Liganden bedeuten, die ausgewählt sind aus Lösungsmitteln, Halogenatomen und Liganden, die eines oder mehrere neutrale Donoratome besitzen, die in der Lage sind, koordinative Bindungen mit dem Radionuklid zu bilden; x und y unabhängig voneinander eine ganz Zahl von 1 bis 8 bedeuten; z und z' unabhängig voneinander 0 oder eine ganze Zahl von 1 bis 7 bedeuten; mit der Maßgabe, daß (xy)+z+z' kleiner oder gleich 8 ist; und n die Ladung des Komplexes angibt und 0 (neutral) oder eine positive oder negative ganze Zahl bedeuten kann.

2. Isonitril-Komplex mit der Formel

$$[A(CNR)_6]^+$$

worin A ein Radionuklid, ausgewählt aus Technetium und ^{188}Re, und R einen organischen Rest bedeutet.

3. Kationischer lipophiler Hexakis t - Butyl - isonitril - Komplex von Technetium.

4. Komplex nach Anspruch 1, worin das Radionuklid ein radioaktives Isotop von Tc ist.

5. Komplex nach Anspruch 1, worin das Radionuklid ein radioaktives Isotop von Re ist.

6. Komplex nach Anspruch 1, worin der Isonitrilligand aliphatisch ist.

7. Komplex nach Anspruch 1, worin der Isonitrilligand ein Kohlenwasserstoff-isonitril ist.

8. Komplex nach Anspruch 1, worin der Isonitrilligand ein gesättigtes Kohlenwasserstoff-isonitril ist.

9. Komplex nach Anspruch 1, worin jede koordinative Stellung des radioaktiven Metalls durch einen Isonitrilliganden aufgefüllt ist.

10. Komplex nach Anspruch 1, worin der Isonitrilligand ein einzähliger Ligand ist.

11. Komplex nach Anspruch 1, worin der Isonitrilligand ein zweizähliger Ligand ist.

12. Komplex nach Anspruch 1, worin der Isonitrilligand ein dreizähliger Ligand ist.

13. Komplex nach Anspruch 1, worin der Komplex ein kationischer lipophiler Komplex ist.

14. Komplex nach Anspruch 1, worin das Radionuklid ein radioaktives Isotop von Tc, Ru, Co, Pt, Fe, Os oder Ir ist.

15. Komplex nach Anspruch 1, worin das Radionuklid ein radioaktives Isotop von W, Re, Fe oder Os ist.

16. Komplex nach Anspruch 1, worin das Radionuklid ein radioaktives Isotop von Cr, Mo, Co, Tc, Fe, Mn, W, Ru, Ni, Rh, Ir, Pd, Nb oder Ta ist.

17. Reagenziensatz zur Herstellung eines Koordinationskomplexes gemäß den Ansprüchen 1 bis 3, wobei der Reagenziensatz eine vorgegebene Menge des Isonitrilliganden und eine vorgegebene Menge eines Reduktionsmittels enthält, das in der Lage ist, einj vorgegebene Menge eines aus dem Radionukliden vorausgewählten Radionuklids zur Bildung des Komplexes zu reduzieren.

18. Reagenziensatz nach Anspruch 17, worin der Isonitrilligand und das Reduktionsmittel lyophilisiert vorliegen.

19. Reagenziensatz nach Anspruch 17, worin der lyophilisierte Isonitrilligand und das Reduktionsmittel in einem hermetisch verschlossenen, sterilisierten Behälter enthalten sind.

20. Reagenziensatz nach Anspruch 17, 18 oder 19, worin das vorausgewählte Radionuklid ein Isotop von Tc ist.

21. Reagenziensatz nach Anspruch 17, 18 oder 19, worin das vorausgewählte Radionuklid ein Isotop von Re ist.

22. Reagenziensatz zur Umsetzung eines Vorrates von ^{99m}Tc-Pertechnetat in einen Komplex nach Anspruch 1 bis 3, wobei der Reagenziensatz einen Vorrat eines Isonitrils und einen Vorrat eines Reduktionsmittels, das in der Lage ist das Technetium zu reduzieren, enthält.

23. Reagenziensatz nach Anspruch 22, worin das Reduktionsmittel aus Dithioniten und Zinnsalzen ausgewählt ist.

24. Reagenziensatz nach Anspruch 22, worin der Isonitrilligand und das Reduktionsmittel lyophilisiert sind.

25. Reagenziensatz nach Anspruch 22, worin der lyophilisierte Isonitrilligand und das Reduktionsmittel in einem hermetisch verschlossenen, sterilisierten Behälter enthalten sind.

26. Reagenziensatz nach Anspruch 17, worin das Radionuklid ein radioaktives Isotop von Tc, Ru, Co, Pt, Fe, Os oder Ir ist.

27. Reagenziensatz nach Anspruch 17, worin das Radionuklid in radioaktives Isotop von W, Re, Fe od r Os ist.

28. Reagenzi nsatz nach Anspruch 17, worin das Radionuklid ein radioaktives Isotop von Cr, M , Co, Tc, Fe, Mn, W, Ru, Ni, Rh, Ir, Pd, Nb oder Ta ist.

29. Verfahren zur Markierung von Zellen der Liposomen, bei dem man die Zellen oder Liposomen mit einem Koordinati nskomplex gemäß Anspruch 1 in einem geeigneten Medium inkubiert.

Revendications

1. Compl xe isonitrile répondant à la formule:

$$[A((CN)_xR)_yB_zB'_{z'}]n$$

dans laquelle A est un radionucléide choisi parmi les isotopes radioactifs de Tc, Ru, Co, Pt, Fe, Os, Ir, W, Re, Cr, Mo, Mn, Ni, Rh, Pd, Nb et Ta; $(CN)_xR$ est un ligand isonitrile monodenté ou polydenté, lié au radionucléide par l'intermédiaire de l'atome de carbone du groupe CN; R est un radical organique; B et B' sont indépendamment d'autres ligands choisis parmi les solvants, les atomes d'halogène et les ligands comprenant 1 ou plusieurs atomes donneurs neutres capables de former des liaisons de coordination avec ledit radionucléide; x et y sont chacun indépendamment des nombres entiers de 1 à 8; z et z' sont chacun indépendamment 0 ou un nombre entier de 1 à 7; à condition que (xy)+z+z' soit inférieure ou égale à 8; et n indique la charge du complexe et peut être égal à 0 (neutre) ou à un nombre entier positif ou négatif.

2. Complexe isonitrile répondant à la formule:

$$[A(CNR)_6]^+$$

dans laquelle A est un radionucléide choisi parmi le technétium et le ^{188}Re, et R est un radical organique.

3. Complexe cationique lipophile hexakis t-butyl isonitrile du technétium.

4. Complexe selon la revendication 1, dans lequel le radionucléide est un isotope radioactif de Tc.

5. Complexe selon la revendication 1, dans lequel le radionucléide est un isotope radioactif de Re.

6. Complexe selon la revendication 1, dans lequel le ligand isonitrile est aliphatique.

7. Complexe selon la revendication 1, dans lequel le ligand isonitrile est un isonitrile d'hydrocarbure.

8. Complexe selon la revendication 1, dans lequel le ligand isonitrile est un isonitrile d'hydrocarbure saturé.

9. Complexe selon la revendication 1, dans lequel chaque position de coordination du métal radioactif est occupée par un ligand isonitrile.

10. Complexe selon la revendication 1, dans lequel le ligand isonitrile est un ligand monodenté.

11. Complexe selon la revendication 1, dans lequel le ligand isonitrile est un ligand bidenté.

12. Complexe selon la revendication 1, dans lequel le ligand isonitrile est un ligand tridenté.

13. Complexe selon la revendication 1, caractérisé en ce que ledit complexe est un complexe lipophile cationique.

14. Complexe selon la revendication 1, caractérisé en ce que le radionucléide est un isotope radioactif de Tc, Ru, Co, Pt, Fe, Os ou Ir.

15. Complexe selon la revendication 1, dans lequel le radionucléide est un isotope radioactif de W, Re, Fe, Os.

16. Complexe selon la revendication 1, caractérisé en ce que le radionucléide est un isotope radioactif de Cr, Mo, Co, Tc, Fe, Mn, W, Ru, Ni, Rh, Ir, Pd, Nb ou Ta.

17. Kit destiné à préparer un complexe de coordination selon les revendications 1 à 3, ce kit comprenant une quantité prédéterminée du ligand isonitrile et une quantité prédéterminée d'un agent réducteur capable de réduire une quantité prédéterminée d'un desdits radionucléides présélectionnée pour former le complexe.

18. Kit selon la revendication 17, caractérisé en ce que le ligand isonitrile et l'agent réducteur sont lyophilisés.

19. Kit selon la revendication 17, caractérisé en ce que le ligand isonitrile et l'agent réducteur lyophilisés sont renfermés dans un récipient stérilisé scellé.

20. Kit selon la revendication 17, 18 ou 19, caractérisé en ce que ledit radionucléide présélectionné est un isotope de Tc.

21. Kit selon la revendication 17, 18 ou 19 caractérisé en ce que ledit radionucléide présélectionné est un isotope de Re.

22. Kit pour convertir une réserve de ^{99m}Tc -pertechnétate en complexe selon l'une des revendications 1 à 3, ce kit comprenant une réserve d'un isonitrile et une réserve d'un agent réducteur capable de réduire le technétium.

23. Kit selon la revendication 22, caractérisé en ce que l'agent réducteur est choisi parmi les dithionites et les sels stanneux.

24. Kit selon la revendication 22, caractérisé en ce que le ligand isonitrile et l'agent réducteur sont lyophilsés.

25. Kit selon la revendication 22, caractérisé en ce que l ligand isonitrile et l'agent réducteur ly phillisés sont renfermés dans un récipient stérilisé scellé.

26. Kit sel n la revendication 17, caractérisé en ce qu l radionucléide est un isot pe radi actif de Tc, Ru, C , Pt, Fe, Os u Ir.

27. Kit sel n la revendication 17, caractérisé en ce que l radionucléide est un isotope radioactif de W, Re, Fe ou Os.

28. Kit selon la revendication 17, caractérisé en ce que le radionucléide est un isotope radioactif de Cr, Mo, Co, Tc, Fe, Mn, W, Ru, Ni, Rh, Ir, Pd, Nb ou Ta.

29. Méthode de marquage d'une cellule ou d'un liposome comprenant l'incubation de la cellule ou du liposome avec un complexe de coordination selon la revendication 1, dans un milieu approprié.